# Chemistry, Manufacturing and Control (CMC) Issues in Radiopharmaceutical Investigational New Drug Applications (INDs)

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# Outline

- IND Regulations & CMC Guidance
- Intermediate (Precursor)
- Radionuclide
- Reference Standard
- Drug Product Composition
- Specifications – Analytical methods
- Other Issues

# IND REQUIREMENTS

- A drug product not previously authorized for marketing in the United States first requires submission of an IND to the FDA
- 21 CFR 312 – IND regulations
- 21 CFR 312.22 – General principles underlying IND submission
- 21 CFR 312.23 – General requirements for IND content and format
- 21 CFR 312.23(a)(7) – Chemistry, Manufacturing and Controls (CMC) information
- 21 CFR 312.6 – Labeling of an investigational new drug

# Resources for IND Applications

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm
  - General guidance on INDs
  - Pre IND and IND meetings
  - Guidance documents for  INDs
  - Laws, regulations and procedures
  - Other useful information

# IND STUDIES AND GUIDANCE (CMC)

- IND Studies:
  - Phase 1 / Exploratory IND
  - Phase 2
  - Phase 3
- Amount and Depth of CMC information depends on the phase of investigation
- Guidance:
  - Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071597.pdf
  - INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070567.pdf
  - IND Meetings for Human Drugs and Biologics Chemistry, Manufacturing and Controls Information
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070568.pdf

# Drug Substance in Radioactive Drug

- Drug substance is entire molecule including the radionuclide
  - Include radionuclide as part of the name and structure.
  - Include relative and absolute stereochemistry, molecular formula and relative molecular mass.
- Elucidation of Structure and Other Characteristics
  - Provide data that establish structure of drug radioactive drug substance
  - Use well-characterized single lot of non-radioactive reference standard (surrogate)
  - Compare radioactive drug substance with the non-radioactive reference standard lot
    - Comparison of method of synthesis
    - Chromatographic mobility involving at least two orthogonal methods
    - Other
  - Include information on other characteristics of radioactive drug substance (some properties may be determined using the non radioactive reference standard lot)
    - Physicochemical properties (solubility, pKa)
    - Specific activity
    - Biological properties

# Precursor (Intermediate)

- If manufactured in house or by a contract manufacturer
  - Include synthetic route used for the clinical lot
  - Include controls for materials
  - Include structure characterization information
    - Provide spectral and other analyses data with interpretation
    - Include information on identification & characterization of stereochemistry, potential for isomerism
    - Include impurity information in clinical and preclinical lots
  - Include specifications including analytical procedures
    - Do not write to TBD (to be determined for an acceptance criterion)
  - Include certificate of analysis for the lot that will be used in clinical studies
  - Include information on container closure, storage and stability

# Precursor (Intermediate)

- When obtained commercially
  - Include certificate of analysis for the lot that will be used in clinical studies
  - Include information on synthesis, if available (DMF)
  - Include acceptance specifications and acceptance procedures
  - Include structure characterization information
    - Provide spectral and other analyses data with interpretation
    - Include information on identification & characterization of stereochemistry, potential for isomerism
  - Include information on storage and stability

# Radionuclide

- Prepared in-house
  - Include method of production
  - Include controls for starting material (target)
- Obtained commercially
  - Provide representative certificate of analyses (COA)
  - Provide acceptance specifications
  - DMF reference (Letter of Authorization)

# Drug Substance Reference Standard

- Non-radioactive drug substance reference standard (when produced in house or by a contract manufacturer)
  - Include method of synthesis used
  - Include structure characterization data of the reference standard (specify batch / lot used)
    - Provide spectral and other analyses data with interpretation
    - Impurities in reference standard
  - Batch analyses data (COA)
  - Storage and stability of the reference standard

# Drug Substance Reference Standard

- When obtained from non-official commercial source
  - Certificate of analysis (COA)
    - Assay
    - Purity
    - How is identity known (structure characterization information)
- Store as recommended by vendor
- Retest date

# Drug Substance Reference Standard

- When obtained from official source
  - USP / NF
- Further identity / structure characterization is not necessary
- Provide copy of official statement certifying it as a standard
- User should ensure that it will fulfill the intended purpose when used in an analytical procedure

# Production of Radioactive Drug Substance

- Include method of synthesis and purification of radioactive drug substance
  - Include controls for raw materials
  - Include details of purification procedure
    - e.g., HPLC chromatogram identifying the peak that is collected
- Can be included in drug product section if drug substance and drug product are produced in a continuous operation

# Description and Composition of the Drug Product

- Description of the dosage form (e.g., injection)
- Composition
  - List of all components (radioactive drug substance and excipients)
  - Their amounts on per unit basis
  - Drug substance should be described in radioactivity units and mass units
  - Function of the component (why each excipient is used?)
  - Reference to their quality standard (e.g., compendial monograph or manufacturer's specifications)
- Description of diluent (if diluent is used compatibility studies should be provided)
- Container closure used

# Drug Product Specifications

- Specifications
  - Provide tests, analytical procedures, and acceptance criteria used to ensure the identity, strength, quality, purity, and potency of the drug product.
  - For acceptance criteria, do not write TBD (to be determined).
- Batch Analyses (results)
  - Include batches made in different types of radio-synthesizers (if used).
  - Provide actual result obtained where a numerical value is obtained. Do not write meets specification.

# Analytical Methods

- Although validation data need not be provided in IND, methods should be capable of providing valid data
- Include sufficient details of analytical procedures
- HPLC, GC methods
  - Include system suitability test(s) and acceptance criteria
  - Include representative chromatograms
    - Identify all the peaks

# Container - Closure / Stability

- Include container-closure information
  - Glass vial
  - Stopper (stopper formulation?)
  - Crimp seal
- Include stability data / information for drug product performed in the specified container closure
  - Data in table format
  - Storage statement and expiration dating period.

# Labeling / Environmental Assessment

- IND label must contain caution statement along with other information- 21CFR312.6(a)
  - "Caution: New Drug - Limited by Federal (or United States) law to investigational use"
- Include claim of categorical exclusion from preparation of EA / EIS
  - a statement of compliance with the categorical exclusion criteria – for IND see 21 CFR 25.31 (e)
  - state that to the applicant's knowledge, no extraordinary circumstances exist.

# Preparation of CMC Section

- IND CMC section may be submitted in CTD (common technical document) format
- Include Index listing all parts with page numbers corresponding to the information
- Document should be paginated sequentially, including appendices

# Conclusion

- Regulations and guidance
- Radioactive drug substance issues
- Radioactive drug product issues

Thank-You